

WHAT IS CLAIMED AS NEW AND IS INTENDED TO BE SECURED BY LETTERS
PATENT IS:

1. A method for producing N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester, comprising:

5 subjecting Aspartame and 3-(3-methoxy-4-hydroxyphenyl)propionaldehyde or derivatives thereof to reductive alkylation in a solvent to produce N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester; and

crystallizing said compound.

10 2. The method as defined in Claim 1, wherein the process for crystallizing said compound comprises any one of the following crystallization methods:

- a. crystallization with a solvent useful for crystallization;
- b. crystallization after extraction with water; and
- c. crystallization after separation of Aspartame.

15 3. A method for purifying N-[N-[3-(3-methoxy-4-hydroxyphenyl) propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester, which comprises:

subjecting N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester comprising at least one compound selected from the group consisting of Aspartame, a peptide derivative, an amino acid, an amino acid derivative, an aldehyde, an acetal and an alcohol derivative as impurity to at least any one of the following

20 crystallization processes:

- a. crystallization with a crystallization solvent;
- b. crystallization after extraction with water; and
- c. in the instance Aspartame is present, crystallization after Aspartame is separated,

to crystallize said compound.

4. The method as defined in Claim 1, wherein the solvent for the reductive alkylation reaction is at least one solvent selected from the group consisting of alcohol(s), tetrahydrofuran, acetonitrile, toluene, acetic acid and acetic acid ester(s), or a mixed solvent which consists of at least one of these organic solvents and water.

5. The method as claimed in Claim 2, wherein said compound is crystallized by a process of concentration or by a process for solvent substitution.

6. The method as claimed in Claim 1, wherein the solvent for crystallization of said compound is at least one solvent selected from the group consisting of alcohol(s), tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic acid and acetic acid ester(s), or a mixed solvent which consists of at least one of these organic solvents and water.

7. The method as claimed in Claim 1, wherein the solvent for crystallization of said compound comprises a solvent which has been used in the reductive alkylation reaction.

8. The method as claimed in Claim 5, wherein the solvent of the substitution aspect of crystallization is at least one solvent selected from the group consisting of alcohol(s), tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic acid and acetic acid ester(s), or a mixed solvent which consists of at least one of these organic solvents and water.

9. The method as claimed in Claim 1, wherein the solvent of the reductive alkylation reaction is alcohol(s) or a mixed solvent of alcohol(s) and water, and the solvent of the crystallization process of the compound is alcohol(s) or a mixed solvent comprising alcohol(s).

10. The method as claimed in Claim 2, wherein the solvent of crystallization after extraction with water is at least one solvent selected from the group consisting of alcohol(s),

tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic acid and acetic acid ester(s), or a mixed solvent which consists of at least one of these organic solvents and water.

11. The method as claimed in Claim 2, wherein the process for extraction with water is conducted with a mixed solvent which consists of water and organic solvent(s), the organic solvent forming a layer which separates from an aqueous layer upon mixture with water, and said N-[N-[3-(3-methoxy-4-hydroxyphenyl) propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester being extracted into the aqueous layer.

12. The method as claimed in Claim 11, wherein said organic solvent(s) is at least one solvent selected from the group consisting of acetic acid ester(s), ether, chloroform, dichloromethane, hexane, toluene, alcohol(s), tetrahydrofuran, acetone, acetonitrile and acetic acid.

13. The method as claimed in Claim 2, wherein the solvent for said crystallization after having separated Aspartame is at least one solvent selected from the group consisting of alcohol(s), tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic acid and acetic acid ester(s), or a mixed solvent which consists of at least one of these organic solvents and water.

14. The method as claimed in Claim 2, wherein said process for separating Aspartame is a process for separating Aspartame by crystallization or precipitation with at least one solvent selected from the group consisting of acetic acid ester(s), ether, chloroform, dichloromethane, hexane, toluene, alcohol(s), tetrahydrofuran, acetone, acetonitrile, acetic acid and water.

15. The method as claimed in Claim 1, wherein said reductive alkylation reaction is conducted in the presence of hydrogen and a catalyst for reductive alkylation, and the solvent for said reaction is at least one organic solvent which dissolves the starting materials or a

mixed solvent of said organic solvents and water, and when an insoluble material is present in the reaction mixture obtained after said reductive alkylation reaction, said insoluble material is separated by filtration.

16. The method as claimed in Claim 1, wherein said derivative of 3-(3-methoxy-4-hydroxyphenyl)propionaldehyde is selected from the group consisting of
5 3-(3-methoxy-4-hydroxyphenyl)-2-propenylaldehyde,
3-(3-methoxy-4-protectedhydroxyphenyl)propionaldehyde,
3-(3-methoxy-4-protectedhydroxyphenyl)-2-propenylaldehyde,
and the acetal(s) derived therefrom.

10 17. The method as claimed in Claim 1, wherein the catalyst for said reductive alkylation reaction is a hydrogenation catalyst and is at least one catalyst selected from the group consisting of palladium, platinum, and rhodium based catalysts.

15 18. The method as claimed in Claim 15, wherein said hydrogen is present at a pressure of 0.1 to 1 MPa.

19. The method as claimed in Claim 1, wherein, in said reductive alkylation reaction, the reaction temperature ranges from 15 to 50 °C, and the reaction time ranges from 2 to 48 hours.

20. The method as claimed in Claim 1, wherein the pH of the reaction solvent for said reductive alkylation reaction ranges from 4 to 6.5.

20 21. The method as claimed in Claim 1, wherein the molar ratio of the Aspartame to said 3-(3-methoxy-4-hydroxyphenyl)propionaldehyde or derivative thereof ranges from 0.5 to 2.

22. The method as claimed in Claim 3, wherein said aldehyde is selected from the

group consisting of:

3-(3-methoxy-4-hydroxyphenyl)propionaldehyde,
3-(3-methoxy-4-hydroxyphenyl)-2-propenylaldehyde,
3-(3-methoxy-4-protectedhydroxyphenyl)propionaldehyde,
5 3-(3-methoxy-4-protectedhydroxyphenyl)-2-propenylaldehyde,

and said acetal comprises any acetal derived from these aldehydes.

23. A N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester in the crystalline form, which is prepared by the process of Claim 1.

24. A N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester in crystalline form, which exhibits X-ray diffraction peaks in at least diffraction angles of 5.55°, 12.25°, 18.5°, 21.1° and 22.45° (2 θ , CuK α ray).

25. The compound as claimed in Claim 24, which is prepared or can be prepared in the method as defined in Claim 1.

26. The compound as claimed in Claim 23, which is obtained upon crystallization of said compound from at least one solvent selected from the group consisting of alcohol(s), tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic acid and acetic acid ester(s), or a mixed solvent which consists of at least one of these organic solvents and water.

27. A sweetening agent, a food and drink, a medicament, a confectionary, a hygienic article, or a sweetened food and drink for mammals comprising the compound as claimed in
20 Claim 23.

28. A sweetener comprising the compound of Claim 23 and at least one adjunct selected from the group consisting of a carrier, a bulking agent and excipient, which is employed in sweetening materials.

29. The method as claimed in Claim 1, wherein said 3-(3-methoxy-4-hydroxyphenyl) propionaldehyde or derivative thereof is prepared by subjecting 3-(3-methoxy-4-hydroxyphenyl)-2-propenylaldehyde or acetal thereof, wherein the hydroxyl group may be protected, to reduction to reduce the double bond of the compound.

5 30. The method as defined in Claim 28, wherein said process for reduction is conducted in the presence of a reduction catalyst or a rhodium based catalyst.

31. The method as claimed in Claim 3, wherein said compound is crystallized by a process of concentration or by a process for solvent substitution.

10 32. The method as claimed in Claim 3, wherein the solvent for crystallization of said compound is at least one solvent selected from the group consisting of alcohol(s), tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic acid and acetic acid ester(s), or a mixed solvent which consists of at least one of these organic solvents and water.

15 33. The method as claimed in Claim 2, wherein the solvent for crystallization of said compound comprises a solvent which has been used in the reductive alkylation reaction.

34. The method as claimed in Claim 31, wherein the solvent of the substitution aspect of crystallization is at least one solvent selected from the group consisting of alcohol(s), tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic acid and acetic acid ester(s), or a mixed solvent which consists of at least one of these organic solvents and water.

20 35. The method as claimed in Claim 2, wherein the solvent of the reductive alkylation reaction is alcohol(s) or a mixed solvent of alcohol(s) and water, and the solvent of the crystallization process of the compound is alcohol(s) or a mixed solvent comprising alcohol(s).

36. The method as claimed in Claim 3, wherein the solvent of crystallization after

extraction with water is at least one solvent selected from the group consisting of alcohol(s), tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic acid and acetic acid ester(s), or a mixed solvent which consists of at least one of these organic solvents and water.

37. The method as claimed in Claim 3, wherein the process for extraction with water
5 is conducted with a mixed solvent which consists of water and organic solvent(s), the organic solvent forming a layer which separates from an aqueous layer upon mixture with water, and said N-[N-[3-(3-methoxy-4-hydroxyphenyl) propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester being extracted into the aqueous layer.

38. The method as claimed in Claim 3, wherein the solvent for said crystallization
10 after having separated Aspartame is at least one solvent selected from the group consisting of alcohol(s), tetrahydrofuran, acetonitrile, toluene, ether, acetone, acetic acid and acetic acid ester(s), or a mixed solvent which consists of at least one of these organic solvents and water.

39. The method as claimed in Claim 3, wherein said process for separating
15 Aspartame is a process for separating Aspartame by crystallization or precipitation with at least one solvent selected from the group consisting of acetic acid ester(s), ether, chloroform, dichloromethane, hexane, toluene, alcohol(s), tetrahydrofuran, acetone, acetonitrile, acetic acid and water.